Exhibit H.

Hirose S, Osher J. Rosen V: Consequences of reperfusion after coronary occlusion. Effects on hemodynamic and regional myocardial metabolic function, Am J Cardiol 33: 69, 1974

35. Bishop SP. White FC, Bloor CM: Regional myocardial blood flow during acute myocardial infarction in the conscious dog. Circ Res 38: 429, 1976

36. Jennings RB. Baum JH, Herdson PB: Fine structural changes in myocardial ischemic injury. Arch Pathol 79: 135, 1965

37. Jennings RB, Ganote CE: Structural changes in myocardium during acute ischemia. Circ Res 34 & 35 (suppl III): III-156, 1974

38. Yokoyama HO, Jennings RB, Clabaugh GF: Histochemical studies of early experimental myocardial infarction. Arch Pathol 59: 347, 1955

39. Herdson PB. Kultenbach JP. Jennings RB: Fine structural changes in dog myocardium during autolysis. Am J Pathol 57: 539, 1969

40. Libby P. Maroko PR, Bloor CM. Sobel BE. Braunwald E: Reduction of experimental myocardial infarct size by corticosteroid administration. J Clin Invest 52: 599, 1973

41. Maroko PR, Libby P, Bloor CM, Sobel BE, Braunwald E: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. Circulation 46: 430, 1972

42. Maroko PR, Libby P, Sobel BE, Bloor CM, Sybers HD, Shell WE, Covell JW, Braunwald E: Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. Circulation 45: 1160, 1972

43. Sugg WL, Webb WR, Ecker: Counterpulsation. Ann Thorac Surg 7: 310, 1969

44. Meerbaum S, Lang T-W, Osher JV, Hashimoto K, Lewis GW, Feldstein C. Corday E: Diastolic retroperfusion of acutely ischemic myocardium. Am J Cardiol 37: 589, 1976

45. Rasmussen MM, Reimer KA, Kloner RA, Jennings RB: Infarct size reduction by propranolol before and after coronary ligation in dogs. Circulation 56: 794, 1977

46. Banka VS, Chadda KD, Helfam RH: Limitations of myocardial revascularization in restoration of regional contraction abnormalities produced by coronary occlusion. Am J Cardiol 34: 164, 1974

Infarct Size Reduction by Propranolol before and after Coronary Ligation in Dogs

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SUMMARY Coronary occlusion in the dog results in irreversible myocardial cell injury which develops first in subendocardial areas of severe ischemia and subsequently spreads into mid and subepicardial areas of moderate ischemia. The effect of propranolol on this progression of ischemic injury was evaluated. Three groups of dogs were studied: 1) untreated, 2) treated with propranolol before and throughout coronary ligation, and 3) treated with propranolol beginning three hours after ligation. Dogs were sacrificed 24 hours after coronary ligation and necrosis was quantitated from histologic sections of transmural slices through the posterior papillary muscle. Propranolol reduced infarct size by preventing necrosis in peripheral (subepicardial) areas of moderately ischemic myocardium. Pretreatment with propranolol reduced necrosis from $85 \pm 3\%$ (untreated) to $52 \pm 4\%$ ($P < 0.05$). Delayed propranolol therapy was about half as effective as pre-treatment and reduced necrosis to $71 \pm 3\%$ ($P < 0.05$). Propranolol also limited microvascular injury so that perfusion defects, detected with the dye thioflavin S, were smaller in treated dogs.

MYOCARDIAL CELL DEATH following acute coronary occlusion, develops first in severely ischemic subendocardial myocardium, and progressively spreads to involve areas of moderately ischemic mid- and subepicardial myocardium.[1, 2] Many studies have supported the idea that this process can potentially be limited by early pharmacologic, mechanical or surgical intervention.[1-7]

Previous studies have demonstrated that β-blockade with propranolol or practolol reduces epicardial or precordial ST segment elevation following experimental coronary occlusion or following myocardial infarction in man.[8-10] Histologic studies of necrosis following temporary coronary occlusions have provided direct demonstration that propranolol delays cell death in areas of severe ischemia.[11,12]

The present study was done to determine whether necrosis within the peripheral, moderately ischemic zone of infarcts produced by permanent coronary ligation in dogs could be

limited by propranolol. Infarct size was significantly reduced by propranolol therapy instituted prior to, and maintained throughout coronary occlusion. Intervention with propranolol three hours after coronary ligation was less effective but still produced a significant reduction in infarct size.

Materials and Methods

Mongrel dogs of both sexes weighing 9–28 kg were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and ventilated with a Harvard (Model 1063) respirator. Aseptic surgical techniques were used. Lead II of the standard electrocardiogram (ECG) and peripheral blood pressure, via a catheter in the right femoral artery, attached to a Statham (P23AC) pressure transducer, were monitored on a Grass (Model 5) polygraph. The right saphenous vein was catheterized for propranolol or saline infusion and both catheters were kept open with dilute heparinized saline.

The chest was opened in the fourth left intercostal space, the pericardium was incised, and the circumflex coronary artery was isolated 1–2 cm from the aorta. Dogs in a pretreated group (group B) were given 5 mg/kg propranolol (intra-arterially) 10 min prior to coronary occlusion and an additional 1.0 mg/kg/hr in heparinized saline was infused intravenously at 0.7 cc/min beginning 30 min after occlusion

and continuing until sacrifice at 24 hours. An untreated group (group A) was given isotonic heparinized saline without propranolol at the same rate and the same routes as dogs in group B. A third group of dogs (group C) was given delayed propranolol therapy beginning with 5.0 mg/kg propranolol three hours after occlusion and followed 30 min later with an intravenous infusion at 1.0 or 2.0 mg/kg/hr until sacrifice.

Permanent occlusions were done by double ligation. Following placement of the first ligature, a catheter was placed in the artery for measurement of peripheral coronary pressure (PCP). The catheter was then removed and the second ligature placed. Incisions were closed and all animals were allowed to recover from anesthesia for 24 hours. Approximately 24 hours after occlusion, dogs were reanesthetized. The fluorescent dye, thioflavin S(TS) (1.0 cc/kg of a 4% solution) was injected intravenously to demonstrate areas with collateral flow (fluorescent) vs. areas with low or no flow (nonfluorescent). Ten to fifteen seconds after TS injection, hearts were excised, cooled in isotonic KCl, opened and photographed. Several transmural longitudinal slices were cut from the posterior papillary muscle (PP). These were phtographed under white light to record grossly necrotic areas and under ultraviolet light to record the gross distribution of fluorescence. The ultraviolet light source was a high intensity mercury Leitz lamp with a Zeiss BG 12 excitation filter and a Y2 yellow filter was used on the camera to exclude reflected blue and ultraviolet light. The transmural papillary muscle slices were fixed in 10% phosphate buffered formalin and histologic sections were prepared from each slice and stained with hematoxylin and eosin (H&E), by the periodic acid Schiff reaction (PAS), and with Heidenhain's variant of Mallory's connective tissue stain (CT). Necrosis was quantitated as percent of PP (transmural) by projecting histologic sections of the transmural PP slices onto heavy weight paper, tracing necrotic and spared areas, and cutting and weighing the respective areas of paper. Percent TS nonfluorescence was similarly calculated from the color slides. The groups were compared using the Student's nonpaired *t*-test.

Results

Sixty-nine dogs were used. Sixteen of 33 (48%) untreated controls, 10 of 21 (48%) propranolol pretreated dogs and 10 of 15 (67%) propranolol delayed treated dogs survived the 24 hour period required for analysis of infarct size. Twenty-four dogs that died spontaneously developed ventricular fibrillation, usually during the first few minutes after occlusion. An additional 13 dogs died relatively late after the acute experiment, presumably from arrhythmias although the ECG was not monitored. The number of dogs lost from each group was similar and occurred in an apparently random fashion. We could demonstrate no differences between dogs that lived and those that died when we assessed pre- or post-occlusion heart rate or blood pressure, lead II ST-segment elevation, or exact site of coronary occlusion.

All dogs that survived coronary ligation showed necrosis involving the posterior papillary muscle and surrounding myocardium. The lateral extent of infarction varied from dog to dog depending on coronary anatomy. The transmural extent of necrosis was more consistent within each group,
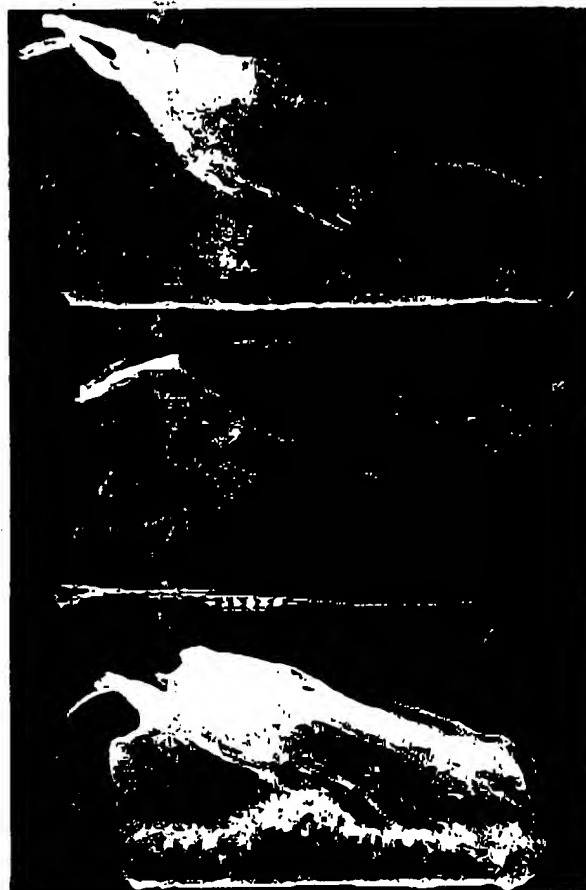

FIGURE 1. *Transmural slices through the ischemic posterior papillary muscles of hearts from representative dogs of each group. All slices are photographed with endocardial surface up and chordae tendineae to the left. a) The top slice is from an untreated dog sacrificed after a 24 hour ligation of the circumflex artery. Necrosis is nearly transmural and consists of a central subendocardial zone (light area) of coagulation necrosis, o hyperemic (dark) midzone and a peripheral zone of necrosis and acute inflammation (light zone). A thin rim of subepicardial muscle (dark) is still viable. b) The middle slice is from a dog pretreated and continuously infused with propranolol and sacrificed after 24 hours of circumflex artery ligation. Necrosis (light areas), with scattered areas of hemorrhage, is present throughout the subendocardial and midmyocardial myocardium. The subepicardial third of the ischemic wall (dark zone) is viable. c) The lower slice is from a dog in which propranolol therapy was delayed until three hours after circumflex coronary ligation. Necrosis involves about three fourths of the transmural thickness and consists of a central core of coagulation necrosis (light). a hyperemic midzone (dark) and a peripheral zone of coagulation necrosis and acute inflammation (light). The subepicardial zone of viable muscle (dark) is intermediate between (a) and (b) in thickness.*

permitting detection of significant differences between treatment groups. Slices through a representative heart from each group is shown in figure 1.

Necrosis was significantly reduced from $85 \pm 4\%$ to $52 \pm 4\%$ of the transmural posterior papillary muscle sections by continuous treatment with propranolol (table 1, fig.

TABLE 1. *Parameters of Ischemic Injury and Collateral Flow in Dogs Surviving 24 Hours Coronary Ligation*

Dog #	Max ST Elevation (mV)	Mean PCP (mm Hg)	% Non-fluorescence	% Necrosis
Untreated				
1774	0.9	—	92	96
1781	0.5	—	71	91
1927	0.4	—	52	71
1870	1.0	—	—	82
1880	0.6	—	—	72
1885	0.1	28	—	87
1889	0.4	23	—	78
1909	1.0	11	—	83
1918	1.0	28	77	72
1937	0.1	—	96	92
1938	0.2	—	—	92
1954	0.9	—	84	96
1959	0.6	28	56	71
2070	0.0	33	94	83
2077	0.3	30	62	93
2116	0.7	8	77	99
Mean ± SE	0.5 ± 0.1	23 ± 3	76 ± 5	85 ± 2
Propranolol Pre-Rx				
1877	0.1	30	17	52
1881	0.1	—	82	47
1890	0.4	18	44	55
1896	0.0	17	84	43
1906	0.1	23	41	40
1934	0.5	—	—	60
1943	0.0	10	73	82
1950	0.1	21	39	50
1955	0.1	28	49	33
1956	0.3	18	39	59
Mean ± SE	0.18 ± 0.06**	21 ± 2	43 ± 5*	52 ± 4***
Propranolol 8 Hr. Delayed Rx				
2061	0.1	—	—	62
2067	1.0	18	69	85
2069	0.2	33	52	73
2072	0.5	16	75	72
2076	0.4	15	76	74
2095	0.5	18	54	69
2086	1.1	18	60	78
2094	0.2	15	44	48
2104	0.6	—	66	73
2107	0.8	18	65	79
Mean ± SE	0.5 ± 0.1	19 ± 2	62 ± 4*	71 ± 3**

*P <0.05; **P <0.01; ***P <0.001 for treated vs. untreated groups compared with the Student's nonpaired t-test.

Abbreviations: Max ST elevation = maximum ST segment elevation in lead II of the standard ECG; PCP = peripheral coronary pressure. Necrosis is expressed as a percentage of transmural sections through the posterior papillary muscle (see methods). SE = standard error of the mean.

FIGURE 2. *Transmural necrosis, calculated as described in the text, is compared in the three treatment groups. Brackets indicate the SEM. Pretreatment and continuous treatment with propranolol during coronary occlusion significantly reduced the transmural extent of necrosis (P < 0.001). Delayed treatment also reduced necrosis (P < 0.01) but was less effective than pretreatment.*

2). Delayed therapy with propranolol started three hours after occlusion resulted in 71 ± 3% necrosis.

The maximum ST-segment elevation in lead II, which usually developed by five minutes after coronary occlusion, also was significantly less in dogs pretreated with propranolol (0.17 mV compared to 0.5 mV in both the untreated and delayed treatment groups) (table 1). Limb lead ST-segment elevation did not accurately reflect subsequent infarct size, however, The linear correlation coefficient for ST elevation (in untreated and propranolol pretreated dogs) vs. ultimate infarct size at 24 hours was only 0.47.
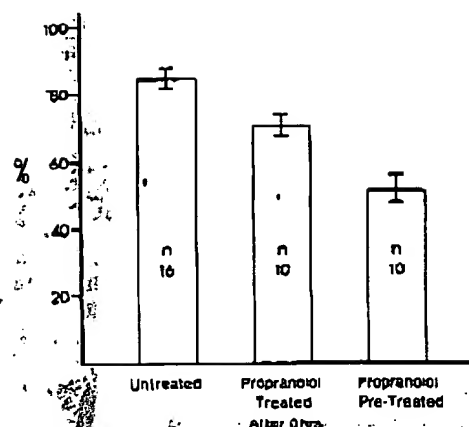
The reduction in myofiber necrosis in propranolol treated dogs was apparently paralleled by smaller areas of microvascular injury. Pale zones of subendocardial myocardium and a surrounding zone of intramural hemorrhage, indicative of vascular damage,[1] were characteristically present in all three groups of dogs (fig. 1). Vascular damage within such areas is supported by the fact that myocardium within these areas was not perfused or stained (was nonfluorescent) after i.v. injection of thioflavin S. However, the amount of nonfluorescent myocardium in the posterior papillary muscle slices was reduced from 76 ± 5% (untreated) to 43 ± 5% by continuous propranolol treatment. The delayed treatment group showed 62 ± 4% nonfluoresence (fig. 3).

Propranolol administration was usually associated with minor reductions in heart rate and mean arterial pressure. However, these parameters varied considerably between dogs, and within each dog over the 24 hr period of study, and no difference between groups was observed (table 2). Most dogs developed frequent ectopic beats and often showed continuous or intermittent runs of ventricular tachycardia. Ectopic activity was biphasic, being prominent in the first half hour, subsiding during the next 2–3 hours and then reappearing and continuing until sacrifice. The heart rate and the percent of total depolarizations which were ectopic on the ECG (in the awake state) 18 hours after occlusion (table 2) were not altered by propranolol treatment.

Discussion

The results obtained from this study demonstrate that propranolol given prior to and continuously during coronary ligation markedly reduces the transmural extent of myocardial infarction. Previous studies have demonstrated that propranolol reduces epicardial ST-segment elevation[9, 10] and delays cell death in areas of severe ischemia so that smaller areas of necrosis occur subsequent to temporary coronary occlusion.[11-13] The present study demonstrates, by direct histologic quantitation, that moderately ischemic cells on

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FIGURE 3.   *Transmural slices through the ischemic posterior papillary muscles of hearts from representative dogs of each group. Each slice was photographed, endocardial surface up, under ultraviolet light after I.V. thioflavin S injection to demonstrate areas of persistent collateral flow (fluorescent, lighter areas) vs. areas with no thioflavin S penetrance (dark areas) and therefore insignificant collateral flow. a) The top slice from an untreated dog shows nearly transmural nonfluorescence. b) The middle slice is from a dog which was pretreated and continuously infused with propranolol. The papillary muscle itself is dark indicating insignificant microvascular perfusion but the outer two thirds of the section has been perfused by thioflavin S indicating microvascular preservation. c) The lower slice from a dog with delayed propranolol treatment demonstrates thioflavin S perfusion and therefore microvascular preservation in the subepicardial half of the section (light zone).*

the subepicardial wavefront of a developing myocardial infarct[1] can be salvaged for at least 24 hours with continuous propranolol therapy. It seems likely that these cells could be salvaged indefinitely since coronary collateral blood flow gradually improves after one to four days of occlusion.[14]

The principal limitation to this type of study is the inability to evaluate necrosis in those dogs that die acutely following coronary occlusion. That this limitation did not alter the conclusions of this study is supported by the facts that 1) mortality was similar in all three groups and 2) deaths were apparently random and could not be predicted from hemodynamic parameters, exact site of coronary occlusion, or magnitude of limb lead ST-segment elevation. The validity of using necrosis in transmural sections through the posterior papillary muscle as an index of infarct size has been shown previously.[1]

The potential for salvage of ischemic myocardium by therapy which is started subsequent to coronary occlusion (the situation which usually would apply in man) depends most importantly on the amount of ischemic but still viable myocardium available at the time therapy is begun. We previously have quantitated transmural necrosis with respect to duration of circumflex coronary occlusion in the dog. Irreversible cell injury in this model develops first in the subendocardial myocardium.[16] A wavefront of cell death then moves from the subendocardial zone of severe ischemia toward the subepicardial zone of more moderate ischemia.[1, 2] By 40 min, about a third of the muscle in transmural sections through the posterior papillary muscle is already dead and becomes necrotic even if reperfusion is allowed. By three hours, an average of 57% of the transmural PP is dead[1] and by 24–96 hours, 85%. Thus, in dogs with circumflex coronary occlusions, there is ischemic myocardium which still is viable at three hours but which, in the absence of therapeutic intervention, dies by 24 hours. This salvageable myocardium includes at three hours (85–57)/85 × 100 or 33% of the 24 hour infarct. Propranolol therapy begun three hours after circumflex ligation salvaged only (85–71)/85 × 100 or 16% of the transmural infarct. However this 16% was about half of the average amount of ischemic muscle estimated to still have been viable and potentially salvageable when therapy was started.

The mechanism by which propranolol reduced the extent of myocardial necrosis is unknown. Dose response studies[18] have indicated that protection is related to β-blockade but have demonstrated maximum effect with the high dose used in the current study. d-propranolol, which shares with d-l-propranolol some direct cardiac depressant effects, is not a β blocker and does not reduce necrosis following temporary ischemic injury.[13]

β-blockade in the anesthetized dog usually reduces heart rate and cardiac contractility and thereby decreases myocardial oxygen demands. Indices of contractility were not obtained in this experiment but heart rate and blood pressure were not significantly different in treated vs. untreated groups. β-blockade has a number of metabolic effects which may be important in delaying cardiac cell injury. These include inhibition of cardiac glycogenolysis and lipolysis[16, 17] and inhibition of Ca++ accumulation by sarcoplasmic reticulum.[18] The role of each of these actions in preserving ischemic myocardium is unknown, however.

TABLE 2.   *Hemodynamic Data*

Group		5-20 min postocol		18 Hr postocol	
		HR	MAP	HR	% Ectopic
A) Untreated		135 ± 23	112 ± 28	194 ± 84	60 ± 37
B) Propranolol Pre-Rx		132 ± 15	101 ± 21	170 ± 12	70 ± 10
C) Propranolol 3 Hr. Delayed Rx		150 ± 43	116 ± 24	176 ± 34	77 ± 13

Abbreviations: HR = heart rate; MAP = mean arterial pressure in mm Hg; % Ectopic = percentage of total beats per minute which were ectopic in the ECG sample taken at 18 hours.

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{"note":"degraded scan"}

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Propranolol reduces total cardiac blood flow and reduces collateral blood flow within subendocardial as well as subepicardial layers of the ischemic myocardium.[19] Subendocardial flow, relative to subepicardial flow, may be unchanged or slightly improved.[19, 20] Collateral blood flow was not directly measured in the present study but peripheral coronary pressure, which has been used as an estimate of potential collateral flow,[14] was similar in treated and untreated dogs. It seems most likely that preservation of ischemic myocardium by propranolol was not related to improved oxygen delivery.

Although muscle cell death precedes microvascular injury, in this model, microvascular necrosis eventually does occur and is associated with interstitial hemorrhage and subendocardial perfusion defects.[1, 21] Any therapeutic intervention which significantly reduces infarct size presumably must prevent necrosis of both cardiac muscle and the vasculature. Results with the dye thioflavin S suggest that propranolol did limit microvascular injury as well as muscle necrosis. This conclusion is supported by ultrastructural analysis and by carbon black labelling studies.[22]

Conclusions and Clinical Implications

This study demonstrates that intervention with propranolol, in dogs with circumflex coronary occlusions, limits infarct size by preventing necrosis of moderately ischemic, subepicardial myocardium peripheral to the central core of the infarct. Although maximum benefit was achieved by initiating propranolol therapy prior to occlusion, some protection occurred when therapy was delayed for three hours. Initial results with low doses of propranolol during uncomplicated myocardial infarction in man have suggested that it reduces ST-segment elevation[9] and improves myocardial metabolism without precipitating congestive heart failure.[9, 23, 24] Propranolol also may prevent clinical infarct extension.[25] However, additional clinical trials will be needed to establish the potential benefits and risk[26-30] of treatment with propranolol during acute myocardial infarction in man.

References

1. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB: The wavefront phenomenon of ischemic cell death. I. Myocardial infarct size vs. duration of coronary occlusion in dogs. Circulation 56: 786, 1977
2. Jennings RB, Reimer KA: Salvage of ischemic myocardium. Mod Concepts Cardiovasc Dis 43: 125, 1974
3. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J, Braunwald E: Factors influencing infarct size following experimental coronary artery occlusions. Circulation 43: 67, 1971
4. Maroko PR, Braunwald E: Modification of myocardial infarction size after coronary occlusion. Ann Intern Med 79: 720, 1973
5. Corday E: Interventions that might influence viability of ischemic jeopardized myocardium. Introduction to symposium on the management of jeopardized ischemic myocardium. Am J Cardiol 37: 461, 1976
6. Ginks WR, Sybers HD, Maroko PR, Covell JW, Sobel BE, Ross J: Coronary Artery Perfusion II. Reduction of Myocardial Infarct Size at 1 week after the Coronary Occlusion. J Clin Invest 51: 2717, 1972
7. Ross J: Early revascularization after coronary occlusion. Circulation 50: 1061, 1974
8. Libby P, Maroko PR, Covell JW, Mallock CI, Ross J, Braunwald E: Effect of practolol on the extent of myocardial ischemic injury after experimental coronary occlusion and its effects on ventricular function in the normal and ischemic heart. Cardiovasc Res 7: 167, 1973
9. Maroko PR, Libby P, Covell JW, Sobel BE, Ross J, Braunwald E: Precordial S-T segment elevation mapping: An atraumatic method for assessing alterations in the extent of myocardial ischemic injury. Am J Cardiol 29: 223, 1972
10. Watanabe T, Shintani F, Fu L, Fujii J, Watanabe H, Kato K: Influence of Inotropic Alteration on the Severity of Myocardial Ischemia after Experimental Coronary Occlusion. Jap Heart J 13: 222, 1972
11. Sommers HM, Jennings RB: Ventricular fibrillation and myocardial necrosis after transient ischemia. Effect of treatment with oxygen, procainamide, reserpine, and propranolol. Arch Intern Med 129: 780, 1972
12. Reimer KA, Rasmussen MM, Jennings, RB: Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. Circ Res 33: 353, 1973
13. Reimer KA, Rasmussen MM, Jennings RB: On the nature of protection by propranolol against myocardial necrosis after temporary coronary occlusion in dogs. Am J Cardiol 37: 520, 1976
14. Bloor CM, White FC: Functional development of the coronary collateral circulation during coronary artery occlusion in the conscious dog. Am J Pathol 67: 483, 1972
15. Jennings RB, Sommers HM, Smyth OA, Flack HA, Linn H: Myocardial Necrosis Induced by Temporary Occlusion of a Coronary Artery in the Dog. Arch Pathol (Chicago) 70: 68, 1960
16. Masters TN, Glaviano VV: Effects of d 1-propranolol on myocardial free fatty acid and carbohydrate metabolism. J Pharmacol Exp Ther 167: 187, 1969
17. Satchell OG, Freeman SE, Edwards SV: Effects of beta-receptor blocking drugs on cardiac metabolism. Biochem pharmacol 17: 45, 1968
18. Hess ML, Briggs FN, Shinebourne E, Hamer J: Effect of adrenergic blocking agents on the calcium pump of the fragmented cardiac sarcoplasmic reticulum. Nature 220: 79, 1968
19. Kloner RA, Reimer KA, and Jennings RB: Distribution of collateral flow in acute myocardial ischemic injury: Effect of propranolol therapy. Cardiovasc Res 10: 81, 1976
20. Pitt B, Craven P: Effect of propranolol on regional myocardial blood flow in acute ischemia. Cardiovasc Res 4: 176, 1970
21. Kloner RA, Ganote CE, Jennings RB: The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 54: 1496, 1974
22. Kloner RA, Fishbein MC, Cotran RS, Braunwald E, Maroko PR: Microvascular injury in acute myocardial ischemia: The effect of propranolol. Am J Pathol 86: 44a, 1977
23. Mueller HS, Ayres S, Religa A, Evans R: Propranolol in the Treatment of Acute Myocardial Infarction. Circulation 49: 1078, 1974
24. Mueller H, Ayres SM: Propranolol in acute myocardial infarction in man: Effects on haemodynamics and myocardial oxygenation. Postgrad Med J 52 (suppl. 4): 141, 1976
25. Pitt B, Weiss JL, Schulze RA, Taylor DR, Kennedy HL, Caralis D: Reduction of myocardial infarct extension in man by propranolol. (abstr) Circulation 53-54 (suppl II): II-29, 1976
26. Bloch A, Beller GA, DeSanctis RW: Chronic propranolol administration and acute myocardial infarction. Am Heart J 92: 121, 1976
27. Snow PJD: Treatment of acute myocardial infarction with propranolol. Am J Cardiol 18: 458, 1966
28. Norris RM, Caughey DE, Scott PJ: Trial of propranolol in acute myocardial infarction. Br Med J 2: 398, 1968
29. Lemberg L, Castellanos A, Arcebal A: The use of propranolol in arrhythmias complicating acute myocardial infarction. Am Heart J 80: 479, 1970
30. Sloman G, Hunt D, Ross D: Propranolol in patients with acute myocardial infarction at the Royal Melbourne Hospital from 1965: A review. Postgrad Med J 52 (suppl. 4): 150, 1976